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Meeting Report

Report on the 6th African Society of Human Genetics (AfSHG) Meeting, March 12–15, 2009, Yaoundé, Cameroon

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Abstract. The African Society of Human Genetics (AfSHG), founded in 2003 with its inaugural meeting in Accra, Ghana,[1] has the stated missions of (1) disseminating information about human genetics research in Africa, (2) establishing a mentorship network providing educational resources, including the development of appropriate technology transfer, (3) providing advocacy for human genetic research in Africa, and (4) encouraging collaborative research. Despite its young age, the AfSHG has developed a strong cadre of active researchers, both within and outside of Africa, with more than 400 members (from 16 countries across Africa as well as 8 other countries), and has held six successful meetings, five in Africa and one in the United States.

INTRODUCTION

The most recent meeting was held in Yaoundé, Cameroon, March 12–15, 2009, coincident with the 1st meeting of the Cameroonian Society of Human Genetics. The scientific program comprised several scientific sessions covering research topics relevant to human genetic research in Africa as well as public health and training. The three keynote speakers were Dr. Sir Richard Roberts, 1993 Nobel Laureate in Medicine and Chief Scientic Officer of New England Biolabs (NEB), Dr. Eric Green, Head of the United States National Human Genome Institute (NHGRI), and Prof. Michael Hayden, Director of the Medical Genetics Department at the University of British Columbia. Dr. Roberts opened the conference with a talk describing his work from the 1970s at Cold Spring Harbour Laboratories, first on restriction endonucleases and then, on adenovirus-2 late mRNA mapping that led to the discovery of RNA splicing. He also gave a brief description on how NEB operates and its commitment to be a community integrated and eco-friendly facility. Dr. Green described the research objectives and capabilities of NHGRI, and Prof. Hayden presented scenarios of how pharmacogenetics research can be and has been performed in settings relevant to sub-Saharan Africa.

The scientific sessions comprised the following topics and some highlights as described below.

HUMAN ORIGINS AND GENETIC DIVERSITY

This session covered topics that included the description of patterns of genetic variation among indigenous South Africans, using high-density genetic data and how such studies can aid in understanding both anthropological diversity within Africa as well as the role of genetics in response to therapeutics, a significantly understudied topic in Africa (Prof. Raj Ramesar, University of Cape Town, Cape Town, South Africa). This talk made a strong case for understanding population structure to analyze complex diseases. Data were presented on five indigenous populations (Herero, San, Sotho/Tswana, Xhosa, and Zulu) that were genotyped using the Affymetrix SNP 6 microarray technology. This chip assays 1.8 million genetic markers [906,600 single nucleotide polymorphisms (SNPs) and more than 946,000 probes for the detection of copy number variation (CNVs)]. Several genomic regions, particularly those subjected to selection, were shown to display population-specific patterns of variation.[2] This led to a conceptual proposal that probing human genetic diversity in health research is essential (e.g., for pharmacogenetic studies of Africans).

Prof. Sarah Tishkoff (University of Pennsylvania, Philadelphia, PA) spoke on "Genotype phenotype analysis of bitter taste perception of phenylthiocarbamide (PTC) in diverse African populations from Cameroon and Kenya." She discussed the process of human adaptation, using, as an example, the type II G protein coupled receptor (*TAS2R38*) gene and PTC tasting. *TAS2R38* was examined in 25 Kenyan and 20 Cameroonian populations, and the data showed a significantly higher level of variation in Africans compared with other world populations as well as signatures of balancing selection or heterozygote advantage. This may indicate that bitter-taste perception is population specific, for reasons yet to be understood.

Prof. Himla Soodyall (University of the Witwatersrand, Witwatersrand, South Africa) presented "Y chromosome DNA variation in Khoe-San and Bantu speaking populations from South Africa." She examined the patterns of genetic variation among Khoe-San in Namibia and South Africa to assess if there is a genetic basis to the linguistic differences of these populations. Her data showed that Khoe-San haplotypes are more similar to Northern Bantu groups. Prof. Soodyall further emphasized the need to share results from African studies to produce a more comprehensive picture of genetic variation and its implications.

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Dr. Rym Kefi Ben-Atig (Pasteur Institute, Tunis, Tunisia) introduced "Mitomedpop," a DNA database that describes and documents mitochondrial DNA (mtDNA) variation. This work catalogues more than 3,000 mtDNA sequences collected from 25 populations from Southern Europe, 12 populations from North Africa, and 3 populations from the Near East.

Ms. Victoria Nembaware (University of Cape Town, Cape Town, South Africa) discussed a "Genome-wide survey of allele-specific alternative splicing in humans." Bioinformatic methods were used to identify 30,977 putative splicing polymorphisms, of which 1,085 were corroborated using public data on 166 lymphoblastoid cell lines. The study provides an extensive resource that can be used to assess the possible effect on splicing of human polymorphisms located in putative splice-regulatory sites.

CANCER

The cancer session included talks that described research in Africans and populations of African descent, and as a group, they provided evidence that more research into genetic and environmental factors that contribute to cancers in Africa is urgently required.

Prof. Muntaser Ibrahim (University of Khartoum, Khartoum, Sudan) discussed the perception of the health burden of cancers in Sudan, with an emphasis on breast cancer and leukemia. This is reflected in the number of graduate students who choose to work on this topic (approximately 40% at the Institute of Endemic Diseases, Khartoum, Sudan). Several research approaches have been undertaken, including analysis of mutations, tumor-associated methylation patterns, alterations in detoxifying pathway genes, causative viral infections, and mitochondrial mutations.

Prof. Franco M. Buonaguro (National Cancer Institute "Fondazione G. Pascale", Naples, Italy) discussed the role of the polymorphism at codon 72 (Arg/Pro) of the *p53* gene in different cancer susceptibilities. His data documented a geographic gradient of this variant with lower frequency of the Arg allele in sub-Saharan populations (Uganda) relative to Caucasians (Italy). The data indicated no association of this variant with human papilloma virus (HPV)-related genital (cervical and penile) squamous cell cancers in either Uganda or Italy. In contrast, ultraviolet (UV) light-related squamous conjunctival cancer from Uganda was associated with HIV infection but not HPV.

Prof. Olufunmilayo Olopade's (University of Chicago, Chicago, IL) presentation on "Early onset breast cancer in African American women" noted the lack of data on the prevalence and incidence of cancer across the African continent and the failure to address how genetics can help understand these conditions at the population level. She advocated the case for genetic screening (e.g., in Nigeria where a limited number of *BRCA1* mutations account for approximately 67% of breast cancers).

Dr. Bamidele Tayo (Loyola University, Maywood, IL) discussed data that showed the presence of both sporadic and Mendelian forms of ovarian cancer using the "Gilda Radner" Familial Ovarian Cancer Registry (based in the United States) that included more than 7,500 individuals. Study of a subgroup showed that *BRCA1/2* mutations could be detected in 39% of the pedigrees. He also argued, based on his data, that mutations in other, as yet unidentified, genes may play a major role in susceptibility to ovarian cancer.

NON-COMMUNICABLE DISEASES

This session was preceded by a presentation entitled "How to fund your research" by Dr. Michael Chew of the Wellcome Trust (London, United Kingdom). Dr. Chew went through a detailed explanation of funding procedures and rationale adopted by the Trust to ensure that the best candidates from African institutions are selected for training in programs developed in strong partnership with United Kingdom research centers.

The non-communicable diseases session included 10 talks that covered topics involving cardiovascular disease and hypertension (Prof. Scott Williams, Vanderbilt University, Nashville, TN; Dr. Bamidele Tayo), diabetes and obesity (Dr. Sonia Abdelhak, Institut Pasteur, Tunis, Tunisia; Dr. Michele Ramsay, University of the Witwatersrand, Witwatersrand, South Africa; Dr. Ayo Doumatey, National Institutes of Health, Bethesda, MD), neurodegenerative diseases (Dr. G. Landoure, University of Bamako, Bamako, Mali); Dr. Sara Ibrahim, University of Gezira, Wad Madni, Sudan), and finally, some aspects of toxicogenomics (Dr. Charles N. Fokunang, University of Yaoundé, Yaoundé, Cameroon). In addition, two additional talks discussed the role that admixture among populations can play in mapping disease genes (Prof. Charles Rotimi, National Institutes of Health, Bethesda, MD) and how genetic data can help elucidate health disparities in populations of the African diaspora (Prof. Georgia Dunstan, Howard University, Washington, DC).

Some highlights of this session include Dr. Tayo's "Genetics of hypertension in Blacks: findings and prospects from studies among Nigerians," which presented preliminary findings of the first genome-wide association study (GWAS) of hypertension in a sub-Saharan African cohort. Several interesting variants were discussed, but the point was made that such findings require a replication cohort; a request was made to AfSHG members and other attendees for collaboration on such a study by sharing DNA resources by forming a consortium among investigators with an interest in hypertension genetics.

Dr. Landoure discussed the topic "Neurogenetics in Mali: where are we?" This presentation emphasized the potential of genetic analyses in identifying factors that affect neurological disease risk in an African context. Mutations were identified in 12 of 27 families studied with neurological diagnosis, and 7 of these families had novel mutations. This work showed the potential to not only replicate previously reported disease genes but also to identify new mutations that may be important in elucidating etiology.

One important conclusion that could be taken from all of talks in this session is that although understanding infectious disease remains critically important to improving the health care of those in sub-Saharan Africa, non-communicable diseases are becoming more prevalent; thus, they are increasingly significant from a public health perspective, and genetics has a central role to play in research on these diseases.

INFECTIOUS DISEASES

The infectious diseases session focused on the genetic susceptibility to bacterial (*Mycobacterium tuberculosis*), parasitic (*Leishmania donovani*), and viral human immunodeficiency virus (HIV) infections and was introduced by a main lecture on "Cancer and infectious diseases" by Prof. Sir Walter Bodmer (Oxford University, Oxford, United Kingdom).

Prof. Bodmer took a historical perspective on the relationship between infection and cancer risk. He presented data indicating that nearly 20% of cancers worldwide are associated with a wide variety of infections, although several different mechanisms are involved in the oncogenic process. For example,

Epstein-Barr virus (EBV) and HPV, DNA viruses associated with Burkitt's lymphoma and cervical carcinoma, respectively, have direct effects on carcinogenesis in ways analogous to oncogenic RNA retroviruses. Other pathogens [e.g., the hepatitis B virus (HBV) in liver cancer and *Helicobacter pylori* in stomach cancer] probably act through inflammatory effects that can provide early stimulus to the outgrowth of a cancer. The role of HIV in cancers secondary to acquired immune deficiency syndrome (AIDS), such as Kaposi's sarcoma, illustrates a third mechanism, namely the role of immune response to viruses such as HPV (e.g., in immunosuppressed kidney-transplant recipients). Finally, Prof. Bodmer emphasized the relevance of cancer-prevention programs, including vaccination against HBV and HPV, particularly in Africa where infection-associated cancers are generally more prevalent than in developed nations.

Prof. William K. Scott (University of Miami, Miami, FL) analyzed the role of pro-inflammatory cytokine polymorphisms on susceptibility to pulmonary tuberculosis (PTB) in two West African populations (The Gambia and Guinea Bissau). Eight polymorphisms in the *IL-12B* gene were examined in the two populations as well as a functional promoter variant in *MCP1*. The overall data provided evidence for the role of *IL-12B* in PTB, confirmed that an *MCP1* promoter variant can influence host susceptibility, and suggested that an interaction between *IL-12B* SNPs and the *MCP1* promoter variant affected disease risk.

Prof. Jennie Blackwell (University of Western Australia, Perth, Western Australia) presented a study on the genetic susceptibility to visceral leishmaniasis (VL). The study focused on Sudanese populations affected by an outbreak of VL caused by the protozoan parasite *Leishmania donovani*. Families from several villages in eastern Sudan were studied using a linkage approach. Linkage to a previously reported locus on 22q12 was not found. Instead, evidence was presented indicating a locus/loci at 1p22 and differences with particular Y chromosome lineages within each village. The results suggested strong lineage-specific VL-associated genes caused by founder effect and consanguinity in recent immigrant populations.

The last three presentations focused on HIV progression risk. Prof. Vittorio Colizzi (University of Rome "Tor Vergata," Italy) described data on the association of human leucocyte antigens (HLA) alleles with progression to AIDS. In a pediatric cohort from Libya, he showed long-term non-progression associated with the *HLA-B58* supertype. In contrast, *HLA-B8* and *HLA-DR3* supertypes associated with progression to AIDS. Dr. Elias F. Onyoh (Cameroon Baptist Convention Health Board HIV/AIDS and Tuberculosis Control Programs, Cameroon) reported on a study that examined the role of chemokine ligand 3-like 1 (*CCL3L1*) gene copy number with HIV-1 in a sample of Sudanese from Khartoum. These data led to the conclusion that copy number lower than the median per diploid genome was associated with increase of HIV-1 infection in people exposed to the virus. Finally, Dr. Judith Torimiro (Center International de Référence "Chantal Biya" pour la Recherche sur la Prévention et la Prise en Charge du Virus de l'Immunodéficience Humaine [VIH]/Syndrome d'Immunodéficience Acquise [SIDA], Yaoundé, Cameroon) presented data on the possible classification of protease and reverse transcriptase genes of HIV-1 isolates from Cameroon. The data clearly showed the need to assess specific HIV-1 genotypic resistance to explain treatment failure and to choose appropriate antiretroviral drug strategies.

MEDICAL GENETICS

The session on Medical Genetics opened with a keynote presentation by Prof. Michael Hayden of the University of British Columbia, Vancouver, Canada. Prof. Hayden focused on the pharmacogenetics of severe adverse drug reactions that cause significant morbidity and mortality. Data were presented showing how biomarkers have been identified for serious adverse drug reactions. The hope, as presented, is to extend work from the developed world to African populations where toxic effects may be more prevalent but are presently undetected.

Prof. Armand Bottani (Geneva Medical School, Geneva, Switzerland) provided an overview of clinical approaches to dysmorphology. He concluded, based on his extensive expertise, that reaching a definitive diagnosis can be challenging and it requires systematic clinical evaluation, but it is essential to help advise families on outcomes and risks for future children.

The question of whether molecular cytogenetics can replace classical chromosomal analysis was addressed by Dr. Frederique Bena (Geneva University Hospital, Geneva, Switzerland). Among the techniques she discussed were comparative genomic hybridization (CGH). Dr. Bena gave examples of how array CGH has been used to detect genomic CNVs in patients with global developmental delay, mental retardation, autism, and multiple congenital anomalies.

The final speaker in this session was Dr. Ambroise Wonkam (local organizer of the meeting, University of Yaoundé, Yaoundé, Cameroon). Dr. Wonkam gave an overview of the practice of medical genetics in a resource-poor setting, using his own experience in Cameroon. He demonstrated that it is possible to develop such a clinical service, although challenges do exist. Dr. Wonkam also presented data showing that Cameroonian medical students and physicians accepted the principles of medical genetics for counseling, pre-natal diagnosis, and in some cases, medical abortion. Of particular interest, parents with a sickle cell anemia-affected child were interested in having pre-natal diagnosis, and the majority would opt for a medical abortion, if a fetus was found to be affected.

ETHNICITY, APPEARANCE, CULTURE, AND GENETICS

The final session of the meeting addressed a broad range of both longstanding and emerging ethical, legal, and social dimensions of genetic and genomic research and practice in Africa.

Prof. Doris Schroeder (University of Central Lancashire, Preston, United Kingdom) discussed the concept sharing benefits derived from research with indigenous populations. She pointed out that the Declaration of Helsinki requires that scientists conducting research with indigenous populations show that the research is of benefit to the target community. She also suggested that decisions about benefit sharing be made before approval of studies and that communities be informed about the outcomes of studies in which they participate. The presentation concluded with a discussion of the potential benefits and challenges of commercialization and patenting, and it emphasized the need for researchers to ensure mutually agreed to benefit, to give feedback, and to establish long-term transparent relationships with communities.

Dr. Ambroise Wonkam described the scope of medical genetics services in Cameroon, which primarily involves prenatal diagnosis for sickle cell disease (SCD). He drew attention to challenges such as limited knowledge of physicians about

genetics, shortage of financial, human, and technical resources for clinical genetics analyses and genetic counseling, and inadequate insurance coverage. Dr. Wonkam also discussed concerns regarding authorship of local investigators on publications, informed consent, export and use of DNA samples, data sharing, capacity building, benefit and harm to participants and communities, and justice in relation to genetic and genomic studies conducted in Cameroon. He stressed the limitations in the number and capability of ethics committees to respond to these and other complex issues raised by molecular and medical genetics, and he called for increased efforts to address these limitations and improve the overall implementation and application of genetic and genomic research in Cameroon and sub-Saharan Africa as a whole.

Dr. Joshua Kimani (University of Nairobi, Nairobi, Kenya) raised a number of issues pertaining to the development of bio-repositories in Africa. He expressed concern that the existing weaknesses in regulatory frameworks needed to govern human subjects research in Africa, coupled with generally low literacy levels and high poverty rates, compromise the ability to deal with the growing interest in developing repositories with samples from Africa. Dr. Kimani highlighted questions about informed consent for present and future studies, recontacting and reconsenting participants, maintenance of privacy and confidentiality, infrastructure for appropriate storage and use of samples, lack of any binding international law on benefit sharing, vulnerability of African scientists, power dynamics among researchers and between researchers and participants, capacity building, ownership of and access to samples, and potential commercialization. He acknowledged that there are only a few bio-repositories in Africa but underscored the need to identify and address the current and potential challenges as the number of these resources increases.

Mr. Vence Bonham (National Institutes of Health, Bethesda, MD) addressed the application of concepts of culture and identity to international large-scale genomic studies. He stated that the primary goal of human genome research is to improve health, and he presented some principles for responsible large-scale studies, including informed participation, respect of individuals' genomes, and promotion of economic development. He talked about identity (ethnic, racial, and national) and culture and their interface with health. Focusing on the labeling of populations, he referred to the United States Census categories frequently used in research, the Indian Genome Variation Project that does not include population labels, and the PhenX project funded by the NHGRI to develop standard measures for collecting demographic and other types of information relevant to GWAS. Mr. Bonham posed several questions for consideration, answers to which could inform study designs and enhance the impact of genomic studies on global health. These include questions about how populations in large-scale studies should be defined and whether there should be international guidelines for the collection and use of ethnic and racial categories in genomic and epidemiological studies.

The session ended with Prof. Michael Parker (Oxford University, Oxford, UK), who drew on his work with the Malaria Genomic Epidemiology Network (MalariaGEN) to discuss ethical dimensions of collaborative global genomics research. He provided a brief introduction to the ethics support program in MalariaGEN, followed by some ethical points to consider when setting up a network involving both developed and developing country partners. Prof. Parker indicated that research funding for networks has increased and that new ethical issues have arisen, largely because of genomics. He discussed challenges including the value, validity, and process of consent. He also talked about the engagement of communities in research, focusing on questions such as: who and what is the community? What engagement methods are appropriate and successful? Who can approve the use of sample collections? What do consent forms say about data release and data sharing? What are the ethical implications of not using collected samples? What are the concerns and implications regarding the shipment of samples? Prof. Parker revisited the discussion of benefit sharing—how we think about benefits and who are the beneficiaries. He ended his presentation with a look at the social value of health-related research and its critical role in guiding the actions of the various stakeholders.

The winners of the Young Investigator Prize 2009 were Dr. Rym Kefi-Ben Atig (Institut Pasteur de Tunis, Tunisia), Dr. Digna Velez (University of Miami, Miami, FL), Dr. Elias F. Onyoh (CBCHB HIV/AIDS and TB Control Programs, Cameroon), and Ms. Victoria Nembaware (University of Cape Town, Cape Town, South Africa).

The meeting was closed by a debate on how to link up to or create web resources to access data generated from African studies and ethical issues around consent for sharing datasets that will require thorough consideration.

The next conference will be held in Cape Town, South Africa, on March 6–9, 2011 (see announcement on www.afshg.org and www.humangenetics2011.org).

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